20030157486 A1
PG Pub 8/21/03, Filing 8/31/01
priority (Pro) 6/21/01.

[0066] B. Fat Metabolism

[0067] The ability to store energy, primarily as fat, is required for the life cycle of higher organisms. Unfortunately, modern life has generated negative consequences of fat storage, obesity. There has been a dramatic worldwide increase in the prevalence of obesity to the point where the majority of adults in America and Europe are considered overweight. Notably, obesity leads to decreased survival as it is associated with the development of many diseases, most notably type II diabetes mellitus, coronary artery disease, hypertension, sleep apnea, arthritis, and even some cancers. In the US alone, estimates indicate that approximately 300,000 people die annually from obesity at a financial cost of more than 100 billion dollars. Globally, over a billion people suffer negative health consequences from excess weight, which is replacing malnutrition and infectious diseases as the most significant cause of illness throughout the world. Therefore, identifying molecules that can alter the ability to store fat has widespread ramifications.

[0068] Historically, the adipocyte has been thought of as a passive conduit i.e., reflecting the amount of food consumed by an organism. However, recent evidence demonstrates that fat storage is under dynamic control and several proteins and hormones are involved in fat metabolism. For example, signals are received on the adipocyte (fat cell) to regulate its actions. In return the adipocyte sends signals, such as a leptin, to other parts of the body to control fat accumulation (Friedman et al., 1998). Recently, another adipocyte-secreted hormone, resistin, was described which was indicated to be a link between obesity and diabetes. For example, blocking resistin function improved blood glucose and insulin resistance in mice with diet-induced obesity (Steppan et al., 2001). Therefore, it seems likely that discovering additional adipocyte-secreted signals may offer potential benefits to the millions of people affected by obesity and diabetes.

[0110] G. Microarray/Chip Technologies

[0111] Specifically contemplated by the present inventors are microarray or chip-based DNA technologies such as those described by Hacia et al. (1996) and Shoemaker et al. (1996). These techniques involve quantitative methods for analyzing large numbers of genes rapidly and accurately. By tagging genes with oligonucleotides or using fixed probe arrays, one can employ chip technology to segregate target molecules as high density arrays and screen these molecules on the basis of hybridization (Pease et al., 1994; Fodor et al., 1991. The present inventors envision that peCAST positive clones will be used to generate PCR fragments to generate a microchip array.

[0112] H. Nucleic Acid Detection

[0113] A variety of nucleic acid detection and/or amplification techniques are suitable for use with the probes and primers that comprise the nucleic acid sequences provided by the present invention in methods for detecting the presence of cancer markers or other proteins comprising a signal- and/or a transmembrane-sequence in a biological sample.

[0114] These embodiments of the invention comprise methods for the identification of cancer cells in biological samples by detecting nucleic acids that correspond to cancer cell markers and are not present in normal cells. The biological sample can be any tissue or fluid in which the cancer cells might have secreted or transmembrane cancer marker protein comprising a signal-sequence. Alternatively, the biological sample can be any tissue or fluid in which the cancer cells might have metastasized to and thus one can detect a cancer marker protein that comprises a transmembrane or secreted sequence.

[0115] Tissue sections, specimens, aspirates and biopsies also may be used. Further suitable examples are bone marrow aspirates, bone marrow biopsies, spleen tissues, fine needle aspirates and even skin biopsies. Other suitable examples are fluids, including samples where the body fluid is peripheral blood, serum, lymph fluid, seminal fluid or urine. Stools may even be used.

[0116] The nucleic acids, used as a template for detection, are isolated from cells contained in the biological sample, according to standard methodologies (Sambrook et al., 1989). The nucleic acid may be genomic DNA or fractionated or whole cell RNA.

[0117] Northern Blotting. In certain embodiments, RNA detection is by Northern blotting, i.e., hybridization with a labeled probe. The techniques involved in Northern blotting are well known to those of skill in the art and can be found in many standard books on molecular protocols (e.g., Sambrook et al., 1989).

[0118] Briefly, RNA is separated by gel electrophoresis. The gel is then contacted with a membrane, such as nitrocellulose, permitting transfer of the nucleic acid and non-covalent binding. Subsequently, the membrane is incubated with, e.g., a labeled probe that is capable of hybridizing with a target amplification product. Detection is by exposure of the membrane to x-ray film, ion-emitting detection devices or colorimetric assays.

[0119] One example of the foregoing is described in U.S. Pat. No. 5,279,721, incorporated by reference herein, which discloses an apparatus and method for the automated electrophoresis and transfer of nucleic acids. The apparatus permits electrophoresis and blotting without external manipulation of the gel and is ideally suited to carrying out methods according to the present invention.

[0120] Reverse Transcriptase PCR.TM.. In other embodiments, RNA detection can be performed using

a reverse transcriptase PCR amplification procedure. Methods of reverse transcribing RNA into cDNA using the enzyme reverse transcriptase are well known and described in Sambrook et al., 1989. Alternative methods for reverse transcription utilize thermostable DNA polymerases. These methods are described in WO 90/07641.

[0121] I. Amplification and Detection

[0122] PCR. In one detection embodiment, DNA is used directly as a template for PCR amplification. In PCR, pairs of primers that selectively hybridize to nucleic acids corresponding to cancer-specific markers are used under conditions that permit selective hybridization. The term primer, as used herein, encompasses any nucleic acid that is capable of priming the synthesis of a nascent nucleic acid in a template-dependent process. Typically, primers are oligonucleotides from ten to twenty-five base pairs in length, but longer sequences can be employed. Primers may be provided in double-stranded or single-stranded form, although the single-stranded form is preferred.

[0123] The primers are used in any one of a number of template-dependent processes to amplify the marker sequences present in a given template sample. One of the best known amplification methods is the polymerase chain reaction (referred to as PCR) which is described in detail in U.S. Pat. No. 4,683,195, 4,683,202 and 4,800,159, each incorporated herein by reference, and in Innis et al. (1990, incorporated herein by reference).

[0124] In PCR, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the cancer marker sequence. The primers will hybridize to form a nucleic acid:primer complex if the cancer marker sequence is present in a sample. An excess of deoxynucleoside triphosphates are added to a reaction mixture along with a DNA polymerase, e.g., Taq polymerase, that facilitates template-dependent nucleic acid synthesis.

[0125] If the marker sequence:primer complex has been formed, the polymerase will cause the primers to be extended along the marker sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the marker to form reaction products, excess primers will bind to the marker and to the reaction products and the process is repeated. These multiple rounds of amplification, referred to as "cycles", are conducted until a sufficient amount of amplification product is produced.

[0126] Next, the amplification product is detected. In certain applications, the detection may be performed by visual means. Alternatively, the detection may involve indirect identification of the product via chemiluminescence, electroluminescence, radioactive scintigraphy of incorporated radiolabel or fluorescent label or even via a system using electrical or thermal impulse signals (Affymax technology).

[0127] A reverse transcriptase PCR amplification procedure may be performed in order to quantify the amount of mRNA amplified. Methods of reverse transcribing RNA into cDNA are well known and described in Sambrook et al., 1989. Alternative methods for reverse transcription utilize thermostable DNA polymerases. These methods are described in WO 90/07641, filed Dec. 21, 1990.

[0128] Other Amplification Techniques. Another method for amplification is the ligase chain reaction ("LCR"), disclosed in European Patent Application No. 320,308, incorporated herein by reference. In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR, bound ligated

units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Pat. No. 4,883,750, incorporated herein by reference, describes a method similar to LCR for binding probe pairs to a target sequence.

[0129] Qbeta Replicase, described in PCT Patent Application No. PCT/US87/00880, also may be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA which has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence which can then be detected.

[0130] An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5-[-thio]-triphosphates in one strand of a restriction site also may be useful in the amplification of nucleic acids in the present invention. Such an amplification method is described by Walker et al. (1992, incorporated herein by reference).

[0131] Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, i.e., nick translation. A similar method, called Repair Chain Reaction (RCR), involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

[0132] Target specific sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having 3 and 5 sequences of non-specific DNA and a middle sequence of specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNase H, and the products of the probe identified as distinctive products which are released after digestion. The original template is annealed to another cycling probe and the reaction is repeated.

[0133] Other amplification methods, as described in British Patent Application No. GB 2,202,328, and in PCT Patent Application No. PCT/US89/01025, each incorporated herein by reference, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (e.g., biotin) and/or a detector moiety (e.g., enzyme). In the latter application, an excess of labeled probes are added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

REFERENCES

[0302] The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

[0303] U.S. Pat. No. 3,817,837

[0304] U.S. Pat. No. 3,850,752

[0305] U.S. Pat. No. 3,939,350

[0306] U.S. Pat. No. 3,996,345

[0307] U.S. Pat. No. 4,196,265

[0308] U.S. Pat. No. 4,275,149

[0309] U.S. Pat. No. 4,277,437

[0310] U.S. Pat. No. 4,366,241

[0311] U.S. Pat. No. 4,472,509

[0312] U.S. Pat. No. 4,683,195

[0313] U.S. Pat. No. 4,683,202

[0314] U.S. Pat. No. 4,800,159

[0315] U.S. Pat. No. 4,816,567

[0316] U.S. Pat. No. 4,867,973

[0317] U.S. Pat. No. 4,883,750

[0318] U.S. Pat. No. 5,021,236

[0319] U.S. Pat. No. 5,279,721

[0320] U.S. Pat. No. 5,536,637

[0321] U.S. Pat. No. 5,565,332

[0322] U.S. Pat. No. 5,925,565

[0323] U.S. Pat. No. 5,928,906

[0324] U.S. Pat. No. 5,935,819

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L1: Entry 1 of 5 File: PGPB Mar 3, 2005

PGPUB-DOCUMENT-NUMBER: 20050049184
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050049184 A1

TITLE: Treatments which elevate functional glycosylated leptin trasnport factor, for controlling weight and obesity

PUBLICATION-DATE: March 3, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Qian, Hao	St. Charles	MO	US
Gingerich, Ronald	St. Charles	MO	US

US-CL-CURRENT: 514/8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw De

☐ 2. Document ID: US 20040158879 A1

L1: Entry 2 of 5 File: PGPB Aug 12, 2004

PGPUB-DOCUMENT-NUMBER: 20040158879
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040158879 A1

TITLE: Polynucleotide and polypeptide fat metabolism regulators and uses thereof

PUBLICATION-DATE: August 12, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Ruvkun, Gary	Newton	MA	US
Ashrafi, Kaveh	San Francisco	CA	US

US-CL-CURRENT: 800/3; 800/8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 3. Document ID: US 20030157486 A1

L1: Entry 3 of 5 File: PGPB Aug 21, 2003

PGPUB-DOCUMENT-NUMBER: 20030157486
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030157486 A1

TITLE: Methods to identify signal sequences

PUBLICATION-DATE: August 21, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Graff, Jonathan M.	Dallas	TX	US
Muenster, Matthew	Irving	TX	US

US-CL-CURRENT: 435/6; 435/252.3, 435/471

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 4. Document ID: US 20020065217 A1

L1: Entry 4 of 5 File: PGPB May 30, 2002

PGPUB-DOCUMENT-NUMBER: 20020065217
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020065217 A1

TITLE: Treatments which elevate functional glycosylated leptin transport factor, for controlling weight and obesity

PUBLICATION-DATE: May 30, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Qian, Hao	St. Charles	MO	US
Gingerich, Ronald	St. Albans	MO	US

US-CL-CURRENT: 514/8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 5. Document ID: US 20040158879 A1, WO 2004007667 A2, AU 2003251809 A1

L1: Entry 5 of 5 File: DWPI Aug 12, 2004

DERWENT-ACC-NO: 2004-180239
DERWENT-WEEK: 200454

TITLE: Novel fat metabolism regulator polypeptide useful for diagnosing, treating or preventing obesity and obesity-related diseases

INVENTOR: ASHRAFI, K; RUVKUN, G

PRIORITY-DATA: 2002US-395159P (July 11, 2002), 2003US-0617351 (July 10, 2003)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20040158879 A1	August 12, 2004		000	A01K067/33
WO 2004007667 A2	January 22, 2004	E	198	C12N000/00
AU 2003251809 A1	February 2, 2004		000	C12N000/00

INT-CL (IPC): A01 K 67/33; C12 N 0/00

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☐	L2	modulator? same fat metabolism	29
☐	L1	microarray same fat metabolism	5

END OF SEARCH HISTORY

COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
017 Public Health, Social Medicine and Epidemiology
030 Pharmacology
022 Human Genetics
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020110
Last Updated on STN: 20020110

AB The aim of this article was to review the evidence for a metabolically normal subset of the obese and its implications for clinical and research work. The methods included literature review and correspondence with authors. Since 1947, when Vague described a relation between distribution of body fat and the risk factors for cardiovascular disease, much evidence has suggested that early onset of the obesity, hyperplasia of normal **adipocytes**, and normal quantities of visceral abdominal fat may be associated with a favorable metabolic response in obese subjects. Analyses in 1973 by Keyes and later by Reuben Andres in 1980 suggested that obesity for some was not a risk factor and might even be an asset. Recently, in the study by Bonora et al of the relation between insulin resistance and the 4 main disorders of the metabolic syndrome in the Bruneck epidemiologic study, a subgroup of obese individuals with a normal metabolic response was evident. In a current study by Brochu et al of an obese metabolically normal subgroup of postmenopausal women, visceral abdominal fat estimated by computed tomography (CT) scan and age of onset were significant variables. The obese, metabolically normal subgroup (OBMN) must be taken into consideration in both clinical and research work. Persons with OBMN and their parents may be wrongly blamed because of the obesity. Attempts at weight loss may be counterproductive. The criteria for selection of obese research subjects may favor inclusion of an OBMN subset, which may invalidate statistical analysis. Findings suggesting the OBMN subset include family members with uncomplicated obesity, early onset of the obesity, fasting plasma insulin within normal range, and normal distribution of the excess fat. Hormonal, genetic studies, and prospective studies will help to clarify the significance and underlying mechanisms of this subset.

L16 ANSWER 16 OF 24 BIOSIS
ACCESSION NUMBER: 2002:261590 BIOSIS
DOCUMENT NUMBER: PREV200200261590
TITLE: **Microarray** analysis of differentiation from MAPC to osteoblasts.
AUTHOR(S): Qi, Huilin [Reprint author]; Aguiar, Dean [Reprint author]; Verfaillie, Catherine [Reprint author]
CORPORATE SOURCE: Medicine, Stem Cell Institute, University of Minnesota, Minneapolis, MN, USA
SOURCE: Blood, (**November 16, 2001**) Vol. 98, No. 11 Part 1, pp. 832a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 May 2002
Last Updated on STN: 1 May 2002

AB Human bone marrow derived multipotent adult progenitor cells (MAPC) differentiate into osteoblasts, chondrocytes, **adipocytes**,

myocytes, endothelial cells and neuronal cells. In order to identify genes involved in commitment of MAPC to osteoblasts, we examined differentially expressed genes by **microarray** analysis in MAPC and MAPC treated with beta-glycerophosphate, Dexamethasone and ascorbic acid to induce the osteoblast phenotype. Total RNA from MAPC isolated from three donors and MAPC induced to osteoblast cell lineage at days 1, 2 and 7 were hybridized to **microarrays** from Research Genetics (4324 human genes). We found that 157 genes are up regulated (gtoreq2 fold), 212 genes are down regulated (gtoreq2 fold) in day 1 differentiated cells. 310 genes are up and 432 are down regulated by day 2; and 787 up and 358 down regulated by day 7. Three transcription factors were up regulated at all three time points: DGSI, which belongs to TBX family and known to have a possible role in osteogenesis, DSIPI and BRCA-1. Some transcription factors were up regulated only on day 1, such as CLIM1, and some were only up regulated on day 2, such as AP-4, USF2, HOXA5, and HOX11. HOX11 is known to play a role in osteogenesis and chondrogenesis. The transcription factors HEMX1, Sox22, short stature homeobox 2 and cbfa3 were up regulated on both days 2 and 7, MSX2, Sox3, Sox4, MEF2b, MEF2D, NFIC and NFIX were among transcription factors up regulated on day 7. MSX2 is required for induction of CbFa1, the master transcription factor for osteoblast differentiation, which did not become up regulated until day 7 (detected by **microarray** analysis and Real Time RT-PCR) and 14 (detected by Real Time RT-PCR). Thirty-seven transcription factors were down regulated during differentiation, including ID3, CA150, Zinc finger proteins 6 and 162, and early growth response 1 which were suppressed at all three time points (days 1, 2, and 7) examined. CITED2 was down regulated at day 2. FUSE1 known to be more active in undifferentiated cells was down regulated at both days 2 and 7. The transcriptional repressor ZF87/MAZ, a known inhibitor of the parathyroid hormone receptor (a critical receptor in osteogenesis) gene expression, was suppressed by day 7 of MAPC differentiation to the osteoblast phenotype. Using Real Time RT-PCR we have confirmed differential expression of >20 genes as detected by **microarray** analysis. As up-regulation of cbfa1 was only seen after 7-14 days, **microarray** analysis of differentiation of MAPC to the osteoblast lineage and other lineages should provide important new insights in the pivotal molecular events required for osteoblast and other differentiation.

L16 ANSWER 17 OF 24 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:186722 BIOSIS
DOCUMENT NUMBER: PREV200200186722
TITLE: Thiazolidinediones: A novel class of agents with anti-myeloma activity.
AUTHOR(S): Mitsiades, Constantine S. [Reprint author]; Mitsiades, Nicholas [Reprint author]; Poulaki, Vasiliki; Treon, Steven P. [Reprint author]; Anderson, Kenneth C. [Reprint author]
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA, USA
SOURCE: Blood, (**November 16, 2001**) Vol. 98, No. 11 Part 1, pp. 376a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
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LANGUAGE: English
ENTRY DATE: Entered STN: 13 Mar 2002
Last Updated on STN: 13 Mar 2002

AB The thiazolidinediones constitute a class of pharmacological agents which are ligands to the nuclear receptor PPAR-gamma (peroxisome proliferator-activated receptor-gamma), and both induce **adipocyte** differentiation and increase insulin sensitivity. Importantly, recent

studies have shown that activity of this class of molecules against solid tumors expressing high levels of PPAR-gamma. In this study we characterize the effect of thiazolidinediones against human multiple myeloma (MM) cells. We documented (by MTT colorimetric survival assay, propidium iodide (PI) staining for cell cycle analysis, annexin V-FITC/PI staining and Apo2.7-PE staining) that ciglitazone, at concentrations relevant to serum levels of diabetic patients treated with standard doses of thiazolidinediones, induced cell cycle arrest and apoptosis of MM patient tumor cells and MM cell lines, which are sensitive or resistant to dexamethasone (Dex), doxorubicin (Dox), melphalan (Mel), mitoxantrone (Mit), Apo2L/TRAIL, thalidomide and its immunomodulatory analogs (IMiDs). Furthermore, ciglitazone was active against tumor cells from patients with Waldenstrom's macroglobulinemia (WM). We investigated whether the sensitivity of MM cells to thiazolidinediones was associated with differential expression of PPAR-gamma, but no correlation was noted between the level of PPAR-gamma, as assessed by immunoblotting analyses and the degree of sensitivity to thiazolidinediones. Moreover, there was no definitive association between PPAR-gamma levels and the sensitivity or resistance of MM cells to Dex, Dox, or thalidomide and its analogs. Of note, certain cell lines resistant to the potent pro-apoptotic stimulus of Apo2L/TRAIL were highly sensitive to thiazolidinediones. The thiazolidinedione-induced effect on the transcriptomic and signaling state profile of MM cells were analyzed by cDNA **microarray** and high-throughpout proteomic analyses of the MM signaling state, respectively. Conventional Western blots confirmed that thiazolidinediones induce phosphorylation of residues Thr446 and Thr451 at the activation loop of the interferon-inducible serine/threonine protein kinase R (PKR), also known as double stranded RNA (dsRNA)-dependent kinase. Phosphorylated (activated) PKR phosphorylates and inactivates the alpha subunit of eukaryotic initiation factor 2 (eIF2-alpha). The thiazolidinedione-induced phosphorylation of PKR, and eIF2alpha leads to inhibition of translation initiation, and may account, at least in part, for the induction of cell cycle arrest/apoptosis by this class of agents. Furthermore, ciglitazone downregulates the expression of intracellular inhibitors of apoptosis, such as FLIP, which contributes to the thiazolidinedione-induced increase of sensitivity of MM cells to pro-apoptotic stimuli, such as Apo2L/TRAIL. Ongoing studies in our Center are characterizing the effect of thiazolidinediones on MM cell growth and survival in the BM milieu in ex vivo and in vivo models, in order to provide the framework for upcoming clinical trials of this novel class of molecules for patients with MM.

L16 ANSWER 18 OF 24 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:151965 BIOSIS
DOCUMENT NUMBER: PREV200200151965
TITLE: Defining the Dexter-type human bone marrow culture system using cDNA **microarray** analysis.
AUTHOR(S): Seshi, Beerelli [Reprint author]; Kumar, Sanjay [Reprint author]; King, Debra [Reprint author]
CORPORATE SOURCE: Interdisciplinary Oncology Program, H. Lee Moffitt Cancer Center, USF, Tampa, FL, USA
SOURCE: Blood, (**November 16, 2001**) Vol. 98, No. 11 Part 2, pp. 146b. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Feb 2002
Last Updated on STN: 26 Feb 2002

AB Dexter-type BM culture system consists of a monolayer of nonhematopoietic stromal cells grown in the presence of hematopoietic cells and

hydrocortisone. Based on Dexter system's ability to support sustained growth and preservation of hematopoietic progenitor cells, it has become the standard in vitro model for the study of hematopoiesis. Its cellular composition has been perceived to be complex, consisting of multiple discrete cell types, including **adipocytes**, fibroblasts, osteoblasts, muscle cells, endothelial cells besides macrophages and hematopoietic cells. This view has given rise to much debate about the relative contributions of various stromal cell populations in hematopoietic supportive function. To address this issue, and also attempt to identify the stromal cell-specific genes, we performed a cDNA analysis of BM stromal cells vs. the starting BM mononuclear cells (MNC) from which the stromal cells were derived. The study involved a cDNA **microarray** etched with apprx4000 known genes and apprx3000 ESTs (Unigem). This study led to identification of 426 stromal-associated genes and 259 MNC-associated genes. Overall apprx9 out of 10 probes tested were confirmed by Northern blotting, validating the **microarray** results. The stromal-associated genes comprised of, (a) lineage-related genes for **adipocytes**, fibroblasts, osteoblasts and muscle cells, and (b) various functional classes of genes. In a separate study including data from a variety of experiments, we accounted for the lineage-related genes by showing the existence of a single unique pluridifferentiated mesenchymal progenitor cell (MPC) type that coexpressed genes for different mesenchymal cell lineages, a possibility heretofore unsuspected (Blood Cells Mol Dis 2000 Jun; 26(3): 234-46; http://www.academicpress.com/bcmd). As a population, MPCs are morphologically and phenotypically about as uniform as any other cell type, e.g., hepatocytes, and can be purified to >95% purity free of macrophages and hematopoietic cells. For results comparing purified MPCs vs. Dexter stroma, see previous reference. The present report concerns investigation of the different functional classes of genes uncovered by the cDNA **microarray** analysis. The classes of genes with abundantly expressed members shown in parenthesis include collagens (type VI alpha3, type I alpha1), laminins (alpha4, beta1, gamma1), proteoglycans (decorin), matrix metalloproteinases (MMP2), apolipoproteins (APO A-1, APO E), growth factors (leptin receptor, fibroblast growth factor 7), annexins (annexin V), galectins (galectin 1), cadherins (CAD11), integrins (beta1, beta5), interleukins (gp130/IL-6 signal transducer), bone morphogenetic proteins (BMP1) and IGF system (IGF2 and IGFBPs 3, 4, 5, 7). The genes of interest also include known cell adhesion molecules (e.g., VCAM 1) as well as CAMs that have heretofore not appreciated to be expressed by BM stromal cells (TGF beta-induced BiGH3, developmental endothelial locus 1 protein (Del-1), lactadherin and epithelial membrane protein 1 (EMP1)). We further undertook a focused investigation of the CAMs using purified MPCs and Northern blotting after treatment of stromal cultures with fibrogenic cytokines TGF beta, PDGF and FGF. Except for up-regulation of BiGH3 by TGF beta, and EMP1 by FGF, overall the results indicate a down-regulation of CAMs by cytokines under study. The lower stromal CAM expression likely contributes to release of immature precursors in chronic myeloproliferative disorders (MPDs) since the cytokines under study have been implicated in MPDs. A searchable WWW-based "Human BM MPC Database" that embodies these and other results from our genomic and proteomic projects is in planning.

L16 ANSWER 19 OF 24 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:441614 BIOSIS
DOCUMENT NUMBER: PREV200100441614
TITLE: Skeletal muscle lipoprotein lipase-mediated resistance to obesity and insulin action results in increased expression of Munc18c.
AUTHOR(S): Schlaepfer, Isabel R. [Reprint author]; Ramanathan, Mathangi [Reprint author]; James, David E. [Reprint author]; Eckel, Robert H. [Reprint author]
CORPORATE SOURCE: Denver, CO, USA
SOURCE: Diabetes, (**June, 2001**) Vol. 50, No. Supplement 2,

pp. A268. print.
Meeting Info.: 61st Scientific Sessions of the American Diabetes Association. Philadelphia, Pennsylvania, USA. June 22-26, 2001. American Diabetes Association.
CODEN: DIAEAZ. ISSN: 0012-1797.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002

L16 ANSWER 20 OF 24 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:307604 BIOSIS

DOCUMENT NUMBER: PREV200100307604

TITLE: Identification of genes responsible for bone differentiation from human bone marrow derived multipotent adult stem cells (MASC).

AUTHOR(S): Qi, Huilin [Reprint author]; Aguiar, Dean [Reprint author]; Verfaillie, Catherine M. [Reprint author]

CORPORATE SOURCE: Stem Cell Institute, Univ. of Minnesota, Minneapolis, MN, USA

SOURCE: Blood, (**November 16, 2000**) Vol. 96, No. 11 Part 1, pp. 70a-71a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 27 Jun 2001
Last Updated on STN: 19 Feb 2002

AB Human bone marrow derived MASC are rare cells that can differentiate into osteoblasts, condrocytes, **adipocytes**, skeletal, smooth and cardiac myocytes, endothelial cells, neurons and glial cells. In order to identify genes involved in commitment of MASC we examined differentially expressed genes in MASC and MASC induced to differentiate to bone for two days. RNA from MASC and MASC induced with beta-glycerophosphate, ascorbic acid and dexamethasone for 2 days were hybridized with **microarrays** from Invitrogen (apprxeq4000 genes). We found that 513/4000 genes were up regulated and 843/4000 down regulated during early bone differentiation. These included: a gtoreq 2 fold increase in expression in day 2 bone of 13/172 transcription factors (e.g. AP-4), 19/225 cytokines and cytokine receptors (e.g. PDGFRB, BMP2), 3/53 cell cycle regulators (e.g. p27), 5/71 matrix proteins (e.g. CRTL1, ECM1). In addition, 20/172 transcription factors (e.g. POU2F2), 25/225 cytokines and receptors (e.g. IL7R), 25/53 cell cycle regulators (e.g. CDC2), 12/71 matrix proteins (e.g. ITGB1) were down regulated gtoreq 2 fold in day 2 bone. Genes known to play an important role in bone differentiation such as bone morphogenetic protein 2 (BMP2) increased about 3.5 fold, and bone proteoglycan II precursor (PGS2) increased about 2.8 fold. We also used subtractive hybridization as a second approach to detect differentially expressed known as well as novel genes. Using the Clontech PCR-Select subtraction method we have detected > 150 genes expressed in day 2 bone but not MASC and > 60 genes in MASC but not day 2 bone. We have sequenced and analyzed 86 individual clones present in day 2 bone but not MASC. Among them we have identified 65 with significant homologies to known proteins like human transmembrane glycoprotein (GPNMB), human HFB 30 (encoding a protein with ring finger motif) and human pigment epithelium-differentiation factor (PEDF). We have also identified 21 clones with homology to EST sequences or with no significant homologies to expressed genes present in any database. Using RT-PCR and quantitative

PCR we have further confirmed that five of these novel genes are up regulated in day 2 bone differentiated from MASC from different bone marrow donors. Studies are ongoing to further analyze the cDNA array data; and to further characterize the potential role in bone differentiation/loss of multipotentiality of known and novel genes identified using these two methods.

L16 ANSWER 21 OF 24 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:403758 BIOSIS
DOCUMENT NUMBER: PREV200000403758
TITLE: Identification of differentially expressed genes from explant cultures of human bone that have undergone adipogenesis.
AUTHOR(S): Nuttall, M. E. [Reprint author]; Wang, F. [Reprint author]; Rieman, D. [Reprint author]; Prichett, W. P. [Reprint author]; Gowen, M. [Reprint author]; Suva, L. J. [Reprint author]
CORPORATE SOURCE: Bone and Cartilage Biology, SmithKline Beecham, King of Prussia, PA, USA
SOURCE: Journal of Bone and Mineral Research, (**September, 2000**) Vol. 15, No. Suppl. 1, pp. S276. print.
Meeting Info.: Twenty-Second Annual Meeting of the American Society for Bone and Mineral Research. Toronto, Ontario, Canada. September 22-26, 2000. American Society for Bone and Mineral Research.
CODEN: JBMREJ. ISSN: 0884-0431.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Sep 2000
Last Updated on STN: 8 Jan 2002

L16 ANSWER 22 OF 24 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:347226 BIOSIS
DOCUMENT NUMBER: PREV200000347226
TITLE: Analysis of human **adipocyte** gene expression using DNA **microarrays**.
AUTHOR(S): Keijer, Jaap; Bakker, Arjen; Kramer, Evelien [Reprint author]; Bouillaud, Frederic; van Hal, Nicole L. W.
CORPORATE SOURCE: RIKILT, Wageningen, Netherlands
SOURCE: International Journal of Obesity, (**May, 2000**) Vol. 24, No. Supplement 1, pp. S132. print.
Meeting Info.: 10th European Congress on Obesity of the European Association for the Study of Obesity. Antwerp, Belgium. May 24-27, 2000. European Association for the Study of Obesity.
CODEN: IJOBDP. ISSN: 0307-0565.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Aug 2000
Last Updated on STN: 7 Jan 2002

L16 ANSWER 23 OF 24 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:344358 SCISEARCH
THE GENUINE ARTICLE: 309YJ
TITLE: Leptin-specific patterns of gene expression in white adipose tissue
AUTHOR: Soukas A; Cohen P; Socci N D; Friedman J M (Reprint)
CORPORATE SOURCE: Rockefeller Univ, Mol Genet Lab, 1230 York Ave, New York, NY 10021 USA (Reprint); Rockefeller Univ, Mol Genet Lab, New York, NY 10021 USA; Rockefeller Univ, Ctr Phys & Biol,

New York, NY 10021 USA; Rockefeller Univ, Howard Hughes Med Inst, New York, NY 10021 USA
COUNTRY OF AUTHOR: USA
SOURCE: GENES & DEVELOPMENT, (**15 APR 2000**) Vol. 14, No. 8, pp. 963-980.
ISSN: 0890-9369.
PUBLISHER: COLD SPRING HARBOR LAB PRESS, 1 BUNGTOWN RD, PLAINVIEW, NY 11724 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 50
ENTRY DATE: Entered STN: 2000
Last Updated on STN: 2000

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Leptin is a hormone that regulates body weight by decreasing food intake and increasing energy expenditure. ob/ob mice carry leptin mutations and are obese and hyperphagic. Leptin administration to lean and ob/ob mice activates a novel metabolic program that depletes adipose tissue. Although this response is physiologically distinct from that evident after food restriction, the molecular nature of these differences is as yet unknown. Expression monitoring of 6500 genes using oligonucleotide **microarrays** in wild-type, ob/ob, and transgenic mice expressing low levels of leptin revealed that differences in ambient leptin levels have dramatic effects on the phenotype of white adipose tissue. These data identified a large number of genes that are differentially expressed in ob/ob mice. To delineate the components of the transcriptional program specifically affected by leptin, the level of the same 6500 genes was monitored in wild-type and ob/ob mice at various times after leptin treatment or food restriction. A novel application of k-means clustering identified 8 clusters of adipose tissue genes whose expression was different between leptin treatment and food restriction in ob/ob mice and 10 such clusters in wild-type experiments. One of the clusters was repressed specifically by leptin in both wild-type and ob/ob mice and included several genes known to be regulated by SREBP-1/ADD1. further studies confirmed that leptin decreases the levels of SREBP-1/ADD1 RNA and transcriptionally active SREBP-1/ADD1 protein in white adipose tissue. Future studies of the molecular basis for the apparent coordinate regulation of the other clusters of leptin-regulated genes may reveal additional mechanisms by which leptin exerts its weight-reducing effects.

L16 ANSWER 24 OF 24 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1999:284837 SCISEARCH
THE GENUINE ARTICLE: 185QU
TITLE: A round-up of new patents and allowances
AUTHOR: ANON
SOURCE: BIOTECHNOLOGY LAW REPORT, (**FEB 1999**) Vol. 18, No. 1, pp. 54-58.
ISSN: 0730-031X.
PUBLISHER: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999

=> s (fatty acid metabolism or fat polypeptide?) and (inhibitor compound? or modulator? or
L17 386 (FATTY ACID METABOLISM OR FAT POLYPEPTIDE?) AND (INHIBITOR COMPO UND? OR MODULATOR? OR ACTIVATOR?)

=> dup rem l17
PROCESSING COMPLETED FOR L17
L18 216 DUP REM L17 (170 DUPLICATES REMOVED)

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=> s l18 and 1990-2001/py
L19         112 L18 AND 1990-2001/PY

=> d his

     (FILE 'HOME' ENTERED AT 13:55:39 ON 21 FEB 2006)

     FILE 'MEDLINE, HCAPLUS, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH' ENTERED AT
     13:56:16 ON 21 FEB 2006
L1           25 S (MODULATOR? OR INHIBITOR? OR ACTIVATOR?) AND (FATTY ACID META
L2           12 DUP REM L1 (13 DUPLICATES REMOVED)
L3           25 S (MODULATOR? OR INHIBITOR? OR ACTIVATOR?) AND (FATTY ACID META
L4           12 DUP REM L3 (13 DUPLICATES REMOVED)
L5          213 S (FATTY ACID METABOLISM OR FAT POLYPEPTIDE?) AND MICROARRAY?
L6          102 DUP REM L5 (111 DUPLICATES REMOVED)
L7           23 S L6 AND 1990-2002/PY
L8           23 FOCUS L7 1-
L9            0 S FAT POLYPEPTIDE? AND MICROARRAY?
L10           0 S FAT POLYNUCLEOTIDE? AND MICROARRAY?
L11          19 S FAT CELL? AND MICROARRAY?
L12          14 DUP REM L11 (5 DUPLICATES REMOVED)
L13           2 S L12 AND 1995-2001/PY
L14         647 S ADIPOCYTE? AND MICROARRAY?
L15         297 DUP REM L14 (350 DUPLICATES REMOVED)
L16          24 S L15 AND 1990-2001/PY
L17         386 S (FATTY ACID METABOLISM OR FAT POLYPEPTIDE?) AND (INHIBITOR CO
L18         216 DUP REM L17 (170 DUPLICATES REMOVED)
L19         112 S L18 AND 1990-2001/PY

=> s l16 and l19
L20           0 L16 AND L19

=> s microarray? and (inhibitor compound? or modulator? or activator?)
L21        4986 MICROARRAY? AND (INHIBITOR COMPOUND? OR MODULATOR? OR ACTIVATOR?
                )

=> dup rem l21
PROCESSING IS APPROXIMATELY  40% COMPLETE FOR L21
PROCESSING IS APPROXIMATELY  78% COMPLETE FOR L21
PROCESSING COMPLETED FOR L21
L22         2938 DUP REM L21 (2048 DUPLICATES REMOVED)

=> s l22 and (obesity or fat cell)
L23          71 L22 AND (OBESITY OR FAT CELL)

=> s l19 and l23
L24           0 L19 AND L23

=> s l23 and modulator?
L25          36 L23 AND MODULATOR?

=> s l25 and 1990-2001/py
L26           3 L25 AND 1990-2001/PY

=> d l26 1-3 ibib ab

L26   ANSWER 1 OF 3  BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-07412  BIOTECHDS
TITLE:            Novel polypeptide and polynucleotide, a member of human mutT
                  GTPase family for diagnosing, treating cellular
                  proliferative, immune, cardiovascular, brain, bone, liver,
                  pain or metabolic disorders and viral diseases;
                     vector-mediated recombinant protein gene transfer and
                     expression in mammal host cell, DNA probe, DNA primer,
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antisense, DNA **microarray** and transgenic animal for disease or disorder diagnosis and genetherapy

AUTHOR: MEYERS R A
PATENT ASSIGNEE: MILLENNIUM PHARM INC
PATENT INFO: WO 2001090374 **29 Nov 2001**
APPLICATION INFO: WO 2000-US16424 22 May 2000
PRIORITY INFO: US 2000-206036 22 May 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-089932 [12]

AB DERWENT ABSTRACT:

NOVELTY - An isolated polypeptide (I) referred as 26493, a member of mutT dGTPase family, comprising a naturally occurring allelic variant of a 404 residue amino acid sequence (S1) encoded by a nucleic acid molecule (NA) which hybridizes to a 1902 or 1212 base pair sequence (S2), all fully defined in the specification or its complement, or a fragment of (I), is new.

DETAILED DESCRIPTION - An isolated polypeptide (I) referred as 26493, a member of mutT dGTPase family, comprising a naturally occurring allelic variant of a 404 residue amino acid sequence (S1) encoded by a nucleic acid molecule (NA) which hybridizes to a 1902 or 1212 base pair sequence (S2), all fully defined in the specification or its complement, or a fragment of (I), is new. (I) is a member of mutT dGTPase family which specifically degrades 8-oxo-dGTP to a monophosphate with the concomitant release of pyrophosphate and is chosen from a fragment of (S1) comprising 15 contiguous amino acids, naturally allelic variant of (S1) encoded by a NA which hybridizes to (S2) under stringent conditions or its complement, and a polypeptide encoded by a nucleic acid (NA) having 80 % sequence identity to (S2). INDEPENDENT CLAIMS are also included for the following: (1) an isolated NA (II) chosen from a NA comprising 80 % identity to (S2), a fragment of 300 nucleotides of (S2), a NA encoding (I) or its fragment comprising 15 contiguous amino acids, and a NA encoding a naturally occurring allelic variant of (I); (2) a host cell (III) (a non-human mammalian cell) containing (II); (3) an antibody (IV) which selectively binds to (I); (4) preparing (I), comprising culturing (III) under expression conditions, and recovering the polypeptide; (5) a kit comprising a compound which selectively binds to (I) or which hybridizes to (II) and instructions for use; (6) detecting (V) the presence of (II) in a sample, by contacting the sample with a NA probe or primer which selectively hybridizes to (II) and determining if the NA probe or primer binds to (II) in the sample; (7) modulating the activity of (I), by contacting (I) or cell expressing (I) with a compound which binds to the polypeptide to modulate the activity of (I); and (8) modulating (VI) the activity of 26493-expressing cell, by contacting the cell with a compound that modulates the activity or expression of (I).

WIDER DISCLOSURE - Disclosed as new are the following: (1) NA constructs comprising (II); (2) vectors comprising (II); (3) isolated NA that are antisense to (II); (4) two-dimensional array having several addresses, each address having unique capture probes; (5) 26493 chimeric or fusion proteins; (6) NA which encodes (IV); (7) vectors and cells comprising (7); (8) cell lines e.g. hybridomas which produce (IV); (9) non-human transgenic animals comprising (II) and population of cells from the animals; (10) computer medium having several digitally encoded data records; (11) analyzing 26493 e.g. analyzing structures, function or relatedness to other NA or amino acid sequences; (12) making a computer readable record of a sequence of a 26493 which include recording the sequence on a computer readable matrix; (13) fragments of (IV); and (14) novel agents identified by screening assays using (I).

BIOTECHNOLOGY - Preparation: (I) is prepared by culturing (III) under conditions in which the NA is expressed. Preferred Polypeptide: (I) further comprises heterologous amino acid sequences. Preferred Nucleic Acid: (II) further comprises a vector nucleic acid sequence and a nucleic acid sequence encoding a heterologous polypeptide. Preferred Method: In (V), the sample comprises mRNA molecules and is contacted with a NA

probe. In (VI), the cell is contacted with a compound such as a peptide, phosphopeptide, small organic molecule, small inorganic molecule or an antibody which is conjugated to a cytotoxin, cytotoxic agent or a radioactive metal ion.

ACTIVITY - Cytostatic; Antiinflammatory; Antidiabetic; Antiarthritic; Antirheumatic; Osteopathic; Neuroprotective; Nootropic; Immunosuppressive; Antipsoriatic; Antithyroid; Dermatological; Antiasthmatic; Antiallergic; Antianemic; Hepatotropic; Ophthalmological; Antiarrhythmic; Hypotensive; Anorectic; Antiatherosclerotic; Cardiant; Vasotropic; Antiulcer; Hypertensive; Antiparkinsonian; Anticonvulsant; Nephrotropic; Immunomodulator; Virucide; Analgesic; Vulnerary. No biological data is given.

MECHANISM OF ACTION - Gene therapy; **Modulator** of expression or activity of (I).

USE - (I) is useful for identifying a compound that modulates the activity of the polypeptide or a compound that binds to (I), by determining if the polypeptide binds to the test compound by direct detection of a test compound/polypeptide binding, by using a competition binding assay or an assay for 26493-mediated nucleotide excision. (IV) is useful for detecting the presence of (I) in a sample. (VI) is useful for modulating the activity of 26493-expressing cell such as cardiovascular, endothelial, kidney, pancreatic, immune or neural cell, preferably a hyperproliferative cell found in a solid, soft tissue tumor or a metastatic lesion. (All claimed). (I) and (II) are useful as diagnostic and therapeutic targets for controlling cellular proliferative and/or differentiative disorders, immune, cardiovascular, brain disorders, disorders associated with bone metabolism, liver, prostate, blood vessels, breast, pain or metabolic disorders and viral diseases. The cellular proliferative and/or differentiative disorders include cancer, carcinoma, leukemia or hematopoietic neoplastic disorder; immune disorders include inflammatory disorders, autoimmune diseases e.g. diabetes mellitus, arthritis, including rheumatoid arthritis, osteoarthritis and psoriatic arthritis, multiple sclerosis, myasthenia gravis, autoimmune thyroiditis, ulcerative colitis, psoriasis, Sjogren's syndrome, dermatitis, Crohn's disease, asthma, allergic asthma, conjunctivitis, aplastic anemia, Grave's disease, chronic active hepatitis, autoimmune uveitis, scleroderma; cardiovascular disorders include arrhythmia, cardiomyopathies, hypertension, atherosclerosis, congestive heart failure, neural disorders, disorders involving glia, perinatal brain injury, cerebrovascular diseases such as hypoxia, ischemia, infarction, including hypotension, infections such as acute meningitis, acquired immunodeficiency syndrome (AIDS)-associated myopathy, transmissible spongiform encephalopathies, demyelinating diseases, such as multiple sclerosis, degenerative diseases such as Alzheimer's disease, Parkinson disease, Pick disease, Huntington's disease; toxic and acquired metabolic diseases including vitamin deficiencies, hypoglycemia, hyperglycemia, hepatic encephalopathy, kidney disorders including cystic diseases of the kidney, glomerular diseases, such as acute proliferative glomerulonephritis, hypercalcemia and nephrocalcinosis, urolithiasis, glomerular lesion associated with systemic diseases such as systemic lupus erythematosus, tumors of the kidney; disorders of the pancreas include pancreatitis, cysts, disorders of the endocrine pancreas such as diabetes mellitus, insulinomas; lung disorders include congenital anomalies, atelectasis, adult respiratory distress syndrome, bronchial asthma, bronchiectasis, hypersensitivity pneumonitis and lung tumors; metabolic disorders include **obesity**, anorexia nervosa, cachexia, lipid disorders and diabetes.

ADMINISTRATION - Administered by parenteral, e.g. intravenous, intradermal, subcutaneous, oral, transdermal, transmucosal or rectal route. Dosage is 0.001-30 mg/kg, preferably 5-6 mg/kg. Antibodies are administered at a dose of 0.1 mg/kg.

EXAMPLE - No relevant example is given.(113 pages)

L26 ANSWER 2 OF 3 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-05440 BIOTECHDS

TITLE: Mutant gamma-aminobutyric acid receptor subunits and DNA molecule, useful for diagnosing epilepsy, Alzheimer's disease, migraine, **obesity**, anxiety, manic depression and schizophrenia;
involving vector-mediated gene transfer for expression in host cell, for use in drug screening, DNA probe, DNA **microarray**, gene therapy, and high throughput screening

AUTHOR: WALLACE R H; MULLEY J C; BERKOVIC S F; HARKIN L A; DIBBENS L M

PATENT ASSIGNEE: BIONOMICS LTD

PATENT INFO: WO 2001098486 **27 Dec 2001**

APPLICATION INFO: WO 2000-AU729 20 Jun 2000

PRIORITY INFO: AU 2001-4953 11 May 2001

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: WPI: 2002-122280 [16]

AB DERWENT ABSTRACT:

NOVELTY - An isolated mammalian polypeptide (I), which is a mutant of gamma-aminobutyric acid (GABA) receptor subunit (the mutation disrupts the functioning of an assembled GABA receptor, its functional fragment or homolog, and creates a phenotype of epilepsy, anxiety, manic depression, phobic obsessive symptoms, Alzheimer's disease, schizophrenia, migraine and/or **obesity**), is new.

DETAILED DESCRIPTION - An isolated mammalian polypeptide (I), which is a mutant of gamma-aminobutyric acid (GABA) receptor subunit (the mutation (e.g. substitutions, deletions, truncations, insertions or rearrangements) disrupts the functioning of an assembled GABA receptor, its functional fragment or homolog, and creates a phenotype of epilepsy, anxiety, manic depression, phobic obsessive symptoms, Alzheimer's disease, schizophrenia, migraine and/or **obesity**), is new. INDEPENDENT CLAIMS are also included for the following: (1) an isolated mammalian DNA molecule (II) encoding (I); (2) an isolated mammalian polypeptide complex, being an assembled GABA receptor including (I); (3) preparing (I); (4) an antibody (III) which is immunologically reactive with (I), but not with a wild-type GABA receptor or its subunit; (5) treating (M1) epilepsy, anxiety, manic depression, phobic obsessive symptoms, Alzheimer's disease, schizophrenia, migraine and/or **obesity**, by administering a wild-type GABA receptor or receptor subunit and/or an isolated DNA molecule encoding a wild-type GABA receptor or receptor subunit, or an agonist, antagonist or **modulator** of the GABA receptor to replace GABA receptor activity, or an agonist, antagonist or **modulator** of mutant GABA receptor to restore GABA receptor activity, or a DNA molecule which is a complement of (II); (6) diagnosing (M2) the above conditions, by obtaining DNA from a subject suspected of having the condition and comparing the DNA sequence of the subunit of GABA receptor to the DNA sequence of the corresponding subunit of the wild-type GABA receptor; (7) a genetically modified non-human animal (IV) transformed with (II); (8) a host cell (V) transformed with (II); and (9) an expression vector (VI) comprising (II).

WIDER DISCLOSURE - Complements of (II) are also disclosed.

BIOTECHNOLOGY - Preparation: (I) is produced by culturing host cells transfected with (VI) under conditions effective for polypeptide production and harvesting the mutant GABA receptor subunit. The method further comprises allowing the mutant GABA subunit and other GABA subunits to assemble into a mammalian GABA receptor and harvesting the assembled receptor (claimed). Preferred Polypeptide: (I) comprises one or more conservative substitutions. The receptor subunit is a gamma-2 or delta-subunit of GABAA receptor and the mutation occurs in an extracellular region or large extracellular loop of the GABAA gamma-2 or delta-subunit. The mutation in gamma-2 subunit abolishes or reduces diazepam potentiation of the GABA response and occurs in benzodiazepine binding domain. The mutation occurs in a large cytoplasmic loop between the third and fourth membrane spanning domain of GABAA gamma-2 subunit.

Preferred Nucleic Acid: (II) comprises one or more additional mutations which are point mutations resulting in conservative amino acid substitutions. Preferred Antibody: (III) is a polyclonal, monoclonal, chimeric, single chain antibody or antibody fragments such as F(ab')2 and Fab. Preferred Non-human Animal: (IV) is a rat, mouse, hamster, guinea pig, rabbit, dog, cat, goat, sheep, pig or non-human primate such as monkey and chimpanzee. Preferred Method: In (M1), the diazepam potentiation is restored, and the receptor function is restored through the incorporation of truncated GABA receptors into the cell membrane. The activity of the subject's functional receptor is increased by introducing a wild-type GABAA gamma- or delta-subunit. (M2) involves sequencing each DNA fragment and comparing the sequences. The DNA fragments are subjected to restriction enzyme analysis or single stranded conformation polymorphism (SSCP) analysis.

ACTIVITY - Anticonvulsant; Tranquilizer; Antimanic; Antidepressant; Nootropic; Neuroprotective; Neuroleptic; Antimigraine; Anorectic.

MECHANISM OF ACTION - Gene therapy; **Modulator** of (I). No supporting data is given.

USE - (I)-(III) are useful in the diagnosis of epilepsy, anxiety, manic depression, phobic obsessive symptoms, Alzheimer's disease, schizophrenia, migraine and/or **obesity**. (III) is useful for treating the above conditions. (I), (IV) and (V) are useful in screening of candidate pharmaceutical agents, where high-throughput screening techniques are employed (claimed). (II) is useful to detect and quantitate gene expression in biological samples. Oligonucleotides or longer fragments derived from (II) are useful as probes in a **microarray** used to monitor the expression level of large number of genes. (IV) is useful for the study of the function of a GABA receptor, to study the mechanism of the disease as related to GABA receptor, for the creation of explanted mammalian cultures which express a mutant GABA receptor and for the evaluation of potential therapeutic interventions.

ADMINISTRATION - No administration details given.

EXAMPLE - Individuals from a family which originated in the United Kingdom were used in genotyping and linkage analysis studies. Of the 29 individuals with a history of seizures, 7 had childhood absence epilepsy (CAE), including 6 with prior febrile seizures (FS). An additional 12 individuals had typical FS and a further 3 had the extended phenotype of febrile seizures plus (FS+). The remaining 7 affected individuals included 1 with a more severe generalized epilepsy phenotype, 1 with temporal lobe epilepsy, and 5 with unclassified epilepsy. Automated genotyping of DNA samples obtained from the family was carried out by the Australian Genome Research Facility. A genome-wide scan of 400 markers spread at an average genetic distance of 10 cM was performed. Lod scores were determined using FASTLINK v4.OP. Two point lod scores were calculated assuming autosomal dominant inheritance, 75% penetrance, a disease allele frequency of 0.0001 and equal marker allele frequencies. Results from the genome screen revealed a linked marker on chromosome 5 (D5S422) that segregated with individuals previously classified as affected (CAE, FS or FS+) with a lod score of 6.06. Recombination between the disease allele and markers D5S2112 and D5S2040 placed the affected gene within a 9.3 cM region on chromosome 5q32-q33. A search of the Human Gene Map revealed a cluster of four gamma-aminobutyric acid type A (GABAA) receptor subunits, alpha-1 (GABRA1), alpha-6 (GABRA6), beta-2 (GABRB2) and gamma-2 (GABRG2), that were positioned close to D5S422 and were considered candidate genes for epilepsy associated mutations. In silico database analysis of the GABRG2 nucleotide sequence enabled the determination of the genomic structure of the gene facilitating the design of primers in the intronic sequence spanning each exon. Single stranded conformation polymorphism (SSCP) analysis of GABRG2 exons followed by sequencing of SSCP bandshifts was performed on individuals from the family to identify disease causing mutations. PCR products showing a conformational change were subsequently sequenced. SSCP analysis and sequencing of exon 2 in this family revealed a G to A nucleotide substitution at position 471 of the GABRG2 gene. The c245G to

A mutation changed a highly conserved arginine amino acid to glutamine at residue 43 (R43Q) of the mature GABRG2 protein or residue 82 (R82Q) of the precursor protein. The R43Q change was detected in all family members carrying the disease associated allele but was not detected in 140 control chromosomes from the normal population. Mutation analysis of GABRG2 in another family in which idiopathic generalized epilepsy was also present, identified a C to T nucleotide change at position 1394 within exon 9 of GABRG2 gene. This mutation changed a highly conserved glutamine amino acid to a stop codon at residue 351 of the mature GABRG2 protein giving rise to a truncated protein missing the fourth membrane spanning domain.(99 pages)

L26 ANSWER 3 OF 3 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2002-01101 BIOTECHDS
TITLE: Reagent and methods of regulating galanin receptor-like G-protein coupled receptors and their regulation for therapeutic purposes e.g. treatment of hypotension and asthma ; for gene therapy, diagnosis, and drug screening
AUTHOR: Ramakrishnan S
PATENT ASSIGNEE: Bayer
LOCATION: Leverkusen, Germany.
PATENT INFO: WO 2001068843 **20 Sep 2001**
APPLICATION INFO: WO 2001-EP2925 15 Mar 2001
PRIORITY INFO: US 2000-251515 7 Dec 2000; US 2000-189898 16 Mar 2000
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2001-582449 [65]
AB Reagents and methods of regulating a galanin receptor-like G-protein coupled receptor for therapeutic purposes are claimed. Also claimed are: an isolated polynucleotide (I) encoding a galanin receptor-like protein selected from one having at least 50% sequence identity to a disclosed 419 amino acid protein sequence, a protein comprising a fully defined 1,549 or 1,260 bp sequence, a polynucleotide which hybridizes under stringent conditions to the disclosed polynucleotides, a polynucleotide which differs from the disclosed sequences due to the degeneration of the genetic code, and a polynucleotide that represents a fragment, derivative or allelic variant; an expression vector containing (I); a host cell; a purified protein encoded by (I); production of the protein; detecting (I) in a biological sample by hybridizing (I) to nucleic acid sample; detecting (I) or the protein by using a specific reagent; a diagnostic kit; drug screening; reducing the activity of the protein by contacting a cell with a reagent binding (I) or the protein; a reagent modulating the activity of the protein or (I); and a pharmaceutical composition of the vector and a reagent. (112pp)

=> s fat cell? and modulator and mRNA level? and 1990-2001/py
L27 2 FAT CELL? AND MODULATOR AND MRNA LEVEL? AND 1990-2001/PY

=> d l27 1-2 ibib ab

L27 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:206558 HCAPLUS
DOCUMENT NUMBER: 129:401
TITLE: Chronic effects of a nonpeptide corticotropin-releasing hormone type I receptor antagonist on pituitary-adrenal function, body weight, and metabolic regulation
AUTHOR(S): Bornstein, S. R.; Webster, E. L.; Torpy, D. J.; Richman, S. J.; Mitsiades, N.; Igel, M.; Lewis, D. B.; Rice, K. C.; Joost, H. G.; Tsokos, M.; Chrousos, G. P.
CORPORATE SOURCE: Developmental Endocrinology Branch, National Institute of Child Health and Human Development, Bethesda, MD, 20892, USA

SOURCE: Endocrinology (1998), 139(4), 1546-1555
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CRH, the principal regulator of the hypothalamic-pituitary-adrenal axis and **modulator** of autonomic nervous system activity, also participates in the regulation of appetite and energy expenditure. Antalarmin, a pyrrolopyrimidine compd., antagonizes CRH type 1 receptor-mediated effects of CRH, including pituitary ACTH release, stress behaviors, and acute inflammation. We administered antalarmin chronically to evaluate its effects on hypothalamic-pituitary-adrenal axis function and metabolic status. Adult male rats were treated twice daily with 20 mg/kg of i.p. antalarmin or placebo over 11 days. The animals were weighed; plasma ACTH, corticosterone, leptin, and blood glucose levels were detd.; and morphometric analyses were performed to det. adrenal size and structure, including sizing, histochem., immunohistochem., and electron microscopy. Leptin mRNA expression in peripheral fat was analyzed by Northern blot. Antalarmin decreased plasma ACTH (mean .+-. SD, 2.62.+-.0.063 pg/mL) and corticosterone concns. (10.21.+-.1.80 .mu.g/dL) compared with those in vehicle-treated rats [resp., 5.3.+-.2.0 ($P < 0.05$) and 57.02.+-.8.86 ($P < 0.01$)]. Antalarmin had no significant effect on body wt., plasma leptin, or blood glucose concns. or **fat cell** leptin **mRNA levels**. The width of the adrenal cortex of animals treated with antalarmin was reduced by 31% compared with that in controls without atrophy of the gland. On the ultrastructural level, adrenocortical cells were in a hypofunctional state characterized by reduced vascularization, increased content of lipid droplets, and tubulovesicular mitochondria with fewer inner membranes. The apoptotic rate was increased in the outer zona fasciculata of animals treated with the antagonist (26.6.+-.3.58%) compared with that in placebo-treated controls (6.8.+-.0.91%). We conclude that chronic administration of antalarmin does not affect body wt., carbohydrate metab., or leptin expression, whereas it reduces adrenocortical function mildly, without anatomical, clin., or biochem. evidence of causing adrenal atrophy. These results are promising for future uses of such an antagonist in the.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 2 OF 2 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:174572 SCISEARCH
THE GENUINE ARTICLE: 403ZR
TITLE: As the proliferation promoter noradrenaline induces expression of ICER (induced cAMP early repressor) in proliferative brown adipocytes, ICER may not be a universal tumour suppressor
AUTHOR: Thonberg H; Lindgren E M; Nedergaard J; Cannon B (Reprint)
CORPORATE SOURCE: Stockholm Univ, Arrhenius Lab F3, Wenner Gren Inst, SE-10691 Stockholm, Sweden (Reprint)
COUNTRY OF AUTHOR: Sweden
SOURCE: BIOCHEMICAL JOURNAL, (**15 FEB 2001**) Vol. 354, Part 1, pp. 169-177.
ISSN: 0264-6021.
PUBLISHER: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON W1N 3AJ, ENGLAND
.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 50
ENTRY DATE: Entered STN: 9 Mar 2001
Last Updated on STN: 9 Mar 2001

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The CREM (cAMP-response-element **modulator**) gene product ICER (induced cAMP early repressor) has been proposed to function as a tumour

(cell proliferation) suppressor. To investigate the generality of this concept, the expression pattern of ICER in brown adipocytes was followed; this was critical because brown adipocytes are one of few cell types in which cAMP is associated positively with cell proliferation but negatively with apoptosis. In response to the physiological stimulus of cold (which induces cell proliferation), ICER **mRNA levels** were increased in brown adipose tissue in vivo. In brown adipocytes in primary culture, ICER gene expression was induced by noradrenaline (norepinephrine) not only in the mature state (where noradrenaline potentiates differentiation), but also in the proliferative state of the cell cultures (where noradrenaline enhances cell proliferation). The induction was mediated via beta -receptors and the cAMP/protein kinase A pathway. The induced ICER appeared to repress its own expression and that of the beta2-adrenoceptor. It is thus evident that also in cell types in which cAMP induces proliferation, and even when these cells are in the proliferative state, ICER expression is induced by the same agents that stimulate proliferation. This can either mean that ICER is not a general tumour suppressor, or that brown adipocytes temporally or spatially avoid this role of ICER.

=> d his

(FILE 'HOME' ENTERED AT 13:55:39 ON 21 FEB 2006)

FILE 'MEDLINE, HCAPLUS, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH' ENTERED AT 13:56:16 ON 21 FEB 2006

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L1          25 S (MODULATOR? OR INHIBITOR? OR ACTIVATOR?) AND (FATTY ACID META
L2          12 DUP REM L1 (13 DUPLICATES REMOVED)
L3          25 S (MODULATOR? OR INHIBITOR? OR ACTIVATOR?) AND (FATTY ACID META
L4          12 DUP REM L3 (13 DUPLICATES REMOVED)
L5         213 S (FATTY ACID METABOLISM OR FAT POLYPEPTIDE?) AND MICROARRAY?
L6         102 DUP REM L5 (111 DUPLICATES REMOVED)
L7          23 S L6 AND 1990-2002/PY
L8          23 FOCUS L7 1-
L9           0 S FAT POLYPEPTIDE? AND MICROARRAY?
L10          0 S FAT POLYNUCLEOTIDE? AND MICROARRAY?
L11         19 S FAT CELL? AND MICROARRAY?
L12         14 DUP REM L11 (5 DUPLICATES REMOVED)
L13          2 S L12 AND 1995-2001/PY
L14        647 S ADIPOCYTE? AND MICROARRAY?
L15        297 DUP REM L14 (350 DUPLICATES REMOVED)
L16         24 S L15 AND 1990-2001/PY
L17        386 S (FATTY ACID METABOLISM OR FAT POLYPEPTIDE?) AND (INHIBITOR CO
L18        216 DUP REM L17 (170 DUPLICATES REMOVED)
L19        112 S L18 AND 1990-2001/PY
L20          0 S L16 AND L19
L21       4986 S MICROARRAY? AND (INHIBITOR COMPOUND? OR MODULATOR? OR ACTIVAT
L22       2938 DUP REM L21 (2048 DUPLICATES REMOVED)
L23         71 S L22 AND (OBESITY OR FAT CELL)
L24          0 S L19 AND L23
L25         36 S L23 AND MODULATOR?
L26          3 S L25 AND 1990-2001/PY
L27          2 S FAT CELL? AND MODULATOR AND MRNA LEVEL? AND 1990-2001/PY
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=> log y

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